IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Patent Application No. 10/526,697

Applicant: Mark E. DUDLEY et al.

Filed: May 5, 2005

TC/AU: 1644

Examiner: Michail A. Belyavskyi

Docket No.: 233876 (Client Reference No. E-275-2002/1-US-02)

Customer No.: 45733

APPELLANTS' AMENDED APPEAL BRIEF

U.S. Patent and Trademark Office
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Dear Sir:

In response to the Notice of Noncompliant Appeal Brief mailed in the above-identified application on December 3, 2009, and in support of the appeal from the final rejection dated December 17, 2008, and further to the Pre-Appeal Brief Request for Review filed May 14, 2009, and the Notice of Panel Decision from Pre-Appeal Brief Review mailed on August 14, 2009, Appellants now submit their Amended Brief. A Notice of Appeal was filed on May 14, 2009.

Real Party In Interest

The patent application that is the subject of this appeal is assigned to the Government of the United States of America, Represented by the Secretary, Department of Health and Human Services.

Related Appeals and Interferences

There are no prior or pending appeals, interferences, or judicial proceedings that are related to, directly affect, be directly affected by, or have a bearing on the decision in this Appeal.

Status of Claims

The patent application as filed included claims 1-36. A restriction requirement was issued and claims 37-40 were added. Claims 1-40 are pending, wherein claims 1-22 have been withdrawn from consideration. No claim is allowed. The final rejection of claims 23-40 is appealed. The claims on appeal appear in the Claims Appendix. Claim 23 is the only pending independent claim under examination and rejected, and thus claim 23 is the only appealed independent claim.

Status of Amendments

All amendments have been entered. No amendment after final rejection was filed.

Summary of Claimed Subject Matter

The claimed invention that is the subject of this appeal relates to a method of promoting the regression of a cancer in a mammal using a combination of immunotherapy and chemotherapy (paragraph [0001]; page 2, lines 1-2). Immunotherapy relates to the treatment of cancer patients by administering immune cells, e.g., T-cells, that specifically recognize a cancer antigen expressed by the cancer cells and mediate the destruction of the cancer cells.

In accordance with the embodiment of the invention according to appealed independent claim 23, the only appealed independent claim, a method of promoting the regression of a cancer in a mammal comprises administering to the mammal nonmyeloablative lymphodepleting chemotherapy and subsequently administering autologous T-cells (specification, ¶ [0011]; page 3, lines 17-18). The autologous T-cells have been previously isolated and selected for highly avid recognition of an antigen of the cancer, the regression of which is to be promoted, by stimulation of the T-cells *in vitro* with the antigen of the cancer, followed by one cycle of rapid expansion using irradiated allogeneic

feeder cells, OKT3 antibody, and IL-2 (specification, ¶ [0011], [0014] -[0016], and [0018]; page 3, lines 17-26; page 4, line 24 to page 5, line 18; and page 5, line 26 to page 7, line 4). The T-cells are modified to express a T-cell growth factor that promotes the growth and activation of the autologous T-cells, or, either concomitantly with the autologous T-cells or subsequently to the autologous T-cells, by the same route or a different route, a T-cell growth factor that promotes the growth and activation of the autologous T-cells is administered (specification, ¶¶ [0011], [0017], and [0021]; page 3, lines 17-29; page 5, lines 19-25; and page 6, lines 14-20). Regression of the cancer in the mammal is promoted (specification, ¶ [0008]; page 3, lines 8-10).

An essential feature of the claimed method is that the T-cells undergo only one cycle of rapid expanision (specification, ¶ [0011]; page 3, lines 17-29; ¶ [0014]; page 4, lines 27-29).

Ground of Rejection to be reviewed on Appeal

The grounds of rejection to be reviewed upon appeal are:

Are claims 23-35, 37 and 38 unpatentable based upon obviousness under 35 USC § 103 over Dudley et al., *J. Immunotherapy* 24: 363-373 (2001) (hereinafter, "Dudley 2001") or WO '97/05239 (hereinafter, "WO '239") in view of U.S. Patent No. 6,447,767 to Slavin et al. (hereinafter, "Slavin") and Riddell et al., *J. Immunol. Method* 128: 189-201 (1990) (hereinafter, "Riddell"), and U.S. Patent 5,126,132 to Rosenberg (hereinafter, "Rosenberg")?

Are claims 36, 39, and 40 unpatentable based upon obviousness under 35 USC § 103 over Dudley 2001 or WO '239 in view of Slavin, Rosenberg, and Riddell, as applied to claims 23-35, 37 and 38 above, and further in view of Kawakami et al. *PNAS* 91: 6458-6462 (1994) (hereinafter, "Kawakami") and Stevens et al. *J. Immunol.*, 154: 762-771 (1995) (hereinafter, "Stevens")?

Argument

Rejections under 35 USC § 103

Claims 23-40

I. The Examiner has not set forth a *prima facie* case of obviousness because the combination of Dudley 2001, WO '239, Slavin, Riddell, Rosenberg, Kawakami, and Stevens fails to teach or suggest a method of promoting the regression of a cancer in a mammal comprising administering T cells which have undergone *one* cycle of rapid expansion, as claimed.

The obviousness rejection cannot stand because the Examiner has not set forth a *prima facie* case of obviousness. A *prima facie* case of obviousness requires that the cited combination of references teach or suggest each and every element of the claims. A *prima facie* case of obviousness has not been made with respect to appealed independent claim 23 because the cited combination of references does not teach or suggest each and every element of independent claim 23.

Appealed claim 23 is directed to a method of promoting the regression of a cancer in a mammal comprising, *inter alia*, administering T cells which have undergone *one* cycle of rapid expansion. The Office Action dated December 17, 2008 acknowledges that Dudley 2001 and WO '239 fail to teach administering T cells which have been subjected to one cycle of rapid expansion, but states (page 5, ¶ 2) that "[a]ll of the claimed elements were known in the prior art."

This is simply incorrect.

The combination of the cited references, Dudley 2001, WO '239, Slavin, Riddell, Rosenberg, Kawakami, and Stevens, fails to teach or suggest a method of promoting the regression of a cancer in a mammal comprising administering T cells which have undergone *one* cycle of rapid expansion, as claimed in claim 23. Because the cited references fail to teach or suggest a method comprising administering T cells which have undergone *one* cycle of rapid expansion, as claimed, the obviousness rejection cannot stand.

A. Riddell teaches away from using one cycle of rapid expansion, as claimed.

Moreover, the obviousness rejection cannot stand because Riddell teaches away from using one cycle of rapid expansion. Riddell teaches that successful adoptive immunotherapy requires large numbers of T-cells, which are obtained through the use of *repetitive* stimulation with anti-CD3:

> Moreover, the application of approaches to adoptive immunotherapy developed in animal models to the treatment of human viral or malignant diseases requires the generation of large numbers of viral or tumor specific T-cells for in vivo administration. Therefore, the use of *repetitive* stimulation with CD3 or anti-CD3 and anti-CD28 was explored as a means of expanding T cell clones to large numbers.

(Riddell, pages 194-195, carryover paragraph, emphasis added). Riddell concludes that "this culture method had the potential to promote growth of antigen-specific T-cell clones in long-term culture to cell numbers sufficient for clinical use in adoptive immunotherapy, without the need for specific Ag stimulation during cell growth" (Riddell, page 195, first full paragraph, right column). While the Examiner indicates "nowhere do Riddell et al. teach that multiple rounds of rapid expansion should be used for adoptive immunotherapy" (page 4, ¶ 4), Riddell specifically teaches *repetitive* stimulation and recommends this method to provide sufficient cell numbers. Thus, in view of Riddell, a single rapid expansion would not be expected to generate large enough numbers of T cells for successful adoptive immunotherapy. Therefore, Riddell teaches away from the use of one cycle of rapid expansion, as claimed, and the obviousness rejection based in whole or in part on Riddell cannot stand.

II. The Appellants' evidence of unexpectedly superior clinical results, long-felt need, and repeated failure of other methods rebuts any alleged *prima facie* case of obviousness.

Even assuming, *arguendo*, that the Examiner has set forth a *prima facie* case of obviousness (which has not been set forth), the Examiner has failed to set forth a valid reason as to why *all of* the rebuttal evidence outlining secondary considerations presented by the appellants fails to rebut any alleged *prima facie* case of obviousness.

In particular, the Examiner fails to give proper consideration to the Declaration under 37 CFR § 1.132 by Dr. Mark E. Dudley (hereinafter, "Dudley Declaration") filed on October 17, 2008 (Exhibit A).

A. The Dudley Declaration evidences that the claimed method provides unexpectedly superior clinical results over prior art methods.

The Examiner has failed to consider the evidence in the form of the Dudley

Declaration, Example 1 of the instant application, and studies published in peer-reviewed journals that show that the presently claimed method provides unexpectedly superior objective clinical responses in patients. As explained by the Dudley Declaration, T-cells underwent *multiple* cycles of rapid expansion in Dudley 2001 and Yee et al., *PNAS,* 99: 16168-73 (2002) (Exhibit B; hereinafter, "Yee"). As explained in Dudley 2001 (see, e.g., p. 370, right col.; p. 371, left col.), Yee (p. 16172, right col.; page 16171, right col.), and the Dudley Declaration (Dudley Dec. ¶¶ 5 - 8), the T-cells of Dudley 2001 and Yee failed to persist in the bloodstream of patients and provided poor objective clinical results as measured by RECIST or WHO criteria. As evidenced by the Dudley Declaration, based on the poor objective clinical results obtained in Dudley 2001 and Yee, one of ordinary skill in the art at the time the instant application was filed would *not* have expected that T-cells that had undergone *only one* cycle of rapid expansion, as claimed, would result in a positive, objective clinical response in patients (Dudley Declaration, ¶¶ 3-9). In response to the repeated failure of other methods using multiple rounds of rapid expansion, one of ordinary skill in the art would logically attempt to improve the persistence and effectiveness of the T-cells by *increasing* the number of cycles of rapid expansion, not *decreasing* the number of cycles to one, as claimed.

However, contrary to the seemingly logical choice to *increase* the number of rounds of rapid expansion, the inventors have, instead, found that reducing the number of cycles of rapid expansion to *one* cycle, as claimed, successfully produces positive, clinical results, as shown, for example, in the study described in Example 1 of the instant application (see also Dudley et al. *Science* 298: 850-854 (2002) (Exhibit C; hereinafter, "Dudley 2002") and Dudley et al., *J. Clin. Oncol.*, 26(32): 5233-5239 (2008) (Exhibit D; hereinafter, "Dudley 2008")) (Dudley Declaration, ¶¶ 10-13).

The Dudley Declaration shows that, contrary to the expectations of one of ordinary skill in the art in view of the poor objective clinical results obtained in Dudley 2001 and Yee, six of 13 patients that were treated with cells that had undergone one cycle of rapid expansion in Example 1 of the instant application had objective clinical responses to treatment and four others demonstrated mixed responses with significant shrinkage of one or more metastatic deposits. Objective tumor regression was seen in the lung, liver, lymph nodes, and intraperitoneal masses, and at cutaneous and subcutaneous sites. Five patients, all with evidence of concomitant cancer regression, demonstrated signs of autoimmune melanocyte

destruction. These results were published in Dudley *Science* 2002 (Dudley Declaration ¶ 11).

The Dudley Declaration also shows that, contrary to the expectations of one of ordinary skill in the art in view of the poor objective clinical results obtained in Dudley 2001 and Yee, the study described in Dudley 2008 in which patients were treated with cells that had undergone one cycle of rapid expansion resulted in objective, clinical responses measured by RECIST criteria in 21 out of the 43 patients (48%) (see, e.g., Table 2). Tumor regression was seen in metastases at virtually all visceral and soft tissue sites including brain. In addition, a majority of patients had detectable levels of transferred cells in circulation at one month after treatment (data not shown in paper) (Dudley Declaration, ¶ 12).

Thus, reducing the number of cycles of expansion to one, as claimed, would be counterintuitive to one of ordinary skill in the art, and illustrates a paradigm shift that is an important contribution over the prior art. In view of these unexpectedly superior clinical results, the obviousness rejection cannot stand.

B. The Dudley Declaration evidences that the claimed method answers a long-felt need in the art.

The Examiner has failed to consider the evidence in the form of Example 1 of the instant application, the Dudley Declaration, and the Dudley 2002 and Dudley 2008 references referred to therein that show that the claimed method answers a long-felt need in the art. As explained above, the Dudley Declaration explains that T-cells underwent *multiple* cycles of rapid expansion in Dudley 2001 and Yee, and that the T-cells of Dudley 2001 and Yee failed to persist in the bloodstream of patients and provided poor objective clinical results as measured by RECIST or WHO criteria (Dudley Dec. ¶¶ 5 - 8). In contrast, the claimed method, in which T-cells undergo *one* cycle of rapid expansion, successfully produces positive objective clinical results in patients as shown, for example, in the study described in Example 1 of the instant application (see also Dudley et al. *Science* 298: 850-854 (2002) (Exhibit C; hereinafter, "Dudley 2002") and Dudley et al., *J. Clin. Oncol.*, 26(32): 5233-5239 (2008) (Exhibit D; hereinafter, "Dudley 2008")) (Dudley Declaration, ¶¶ 10-13). The obviousness rejection cannot stand because the Examiner has failed to consider the evidence that the presently claimed method answers a long-felt need in the art to treat patients.

C. The Dudley Declaration evidences that the claimed method succeeds where other methods have repeatedly failed.

The Examiner has failed to consider the evidence in the form of Example 1 of the instant application, the Dudley Declaration, and the Dudley 2002 and Dudley 2008 references referred to therein that show that the claimed method succeeds where other methods have repeatedly failed. As explained above, other methods (e.g., Dudley 2001 and Yee) use *multiple* cycles of rapid expansion, and the T-cells fail to persist in the bloodstream of patients and provide poor objective clinical results. In contrast, the claimed method, in which T-cells undergo one cycle of rapid expansion, produce positive clinical results in this patient population and, therefore, succeed where other methods have repeatedly failed. The obviousness rejection cannot stand because the Examiner has failed to consider that the Dudley Declaration provides evidence that the presently claimed method succeeds where other methods have repeatedly failed.

III. The Examiner has not adequately addressed the Appellants' argument that the Examiner has failed to set forth a *prima facie* case of obviousness and the Appellants' evidence of unexpectedly superior clinical results, long-felt need, and repeated failure of others.

The Examiner has not adequately addressed the Appellants' arguments and evidence in support of patentability. The Office Action dated December 17, 2008 alleges that the arguments are not persuasive because the applicants have allegedly merely argued against the references individually and not the combination of the references (page 3, ¶ 1). The Office Action dated December 17, 2008 further argues that a specific teaching, suggestion or motivation are not required to support an obviousness rejection, and that obviousness does not require absolute predictability, only a reasonable expectation of success (page 3, ¶¶ 2-4). The Office Action dated December 17, 2008 further alleges that the effects of the claimed method are not surprising because, at the time the invention was made, one of ordinary skill in the art would know that administering to the mammal nonmyeloablative lymphodepleting chemotherapy was a routinely used method to induce donor specific tolerance in a method of treating a cancer patient (page 6, ¶ 3). The Office Action dated December 17, 2008 further alleges that one of skill in the art would expect that administering nonmyeloablative lymphodepleting chemotherapy prior to administering T cells would provide better clinical responses (page 6, ¶ 3).

While the Examiner has alleged that Appellants have merely argued the against the references individually and not against the combination of references, and has also alleged that one of ordinary skill in the art would have had a reasonable expectation of success, Appellants have shown that (a) the combination of references fails to suggest a method of promoting the regression of a cancer in a mammal comprising administering T cells which have undergone *one* cycle of rapid expansion as claimed in claim 23; (b) surprisingly superior results; (c) the claimed method answers a long-felt need in the art; and (d) one of ordinary skill in the art would not have had a reasonable expectation of success in view of the repeated failure of other methods.

Moreover, assuming, *arguendo* that a *prima facie* case of obviousness is established (and, as set forth above, the Appellants submit it has *not* been established by the Examiner), the burden shifts to the Appellant to come forward with arguments and/or evidence to rebut the *prima facie* case. Rebuttal evidence and arguments can be presented in the specification, by counsel, or by way of an affidavit or declaration under 37 CFR 1.132. Relevant rebuttal evidence submitted by the applicant/appellant *must* be given meaningful consideration. *In re Sullivan*, 498 F.3d 1345, 84 USPQ2d 1034 (Fed. Cir. 2007); MPEP § 2145. The Office Actions dated December 17, 2008 and March 20, 2009 have not given the required meaningful consideration.

The counter-arguments by the Examiner ignore the Appellants' arguments and rebuttal evidence in support thereof (in the form of the Dudley Declaration, Example 1 of the specification, and the Dudley 2002 and 2008 references) that the claimed method, in which the T-cells had undergone *only one* cycle of rapid expansion, provides *unexpectedly superior clinical results* over the methods described in the cited references. Thus, an additional issue, which was not addressed by the Examiner, is that the claimed methods produce unexpectedly superior results. Moreover, the Examiner also fails to consider the evidence that the Appellants have also presented with respect to the expectations of one of ordinary skill in the art, long-felt need, and the repeated failure of other methods in the form of the Dudley Declaration and the Dudley 2001 and Yee references referred to therein. Thus, the Appellants have clearly rebutted any alleged *prima facie* case of obviousness, and the obviousness rejection cannot stand.

The Examiner's comments with respect to arguing references individually, predictability, and motivation to modify or combine references (see, e.g., December 17, 2008

Office Action, page 3, ¶¶ 1-4; page 5, ¶ 2; and page 6, ¶ 2) fail to properly consider this rebuttal evidence. Although the Examiner alleges that the addition of nonmyeloablative lymphodepleting chemotherapy does not provide surprisingly superior results, the Examiner completely fails to consider the fact that reducing the number of cycles of rapid expansion to *one*, as claimed, as opposed to increasing the number of cycles of rapid expansion, has, in fact, produced surprisingly superior, objective clinical results, contrary to the expectations of one of ordinary skill in the art. The Examiner also fails to consider that the presently claimed method answers a long-felt need and successfully treats cancer patients as compared to the repeated failure of other methods. Accordingly, the obviousness rejection cannot stand.

The commonly accepted wisdom at the time the application was filed was to administer T cells that had undergone *multiple rounds* of rapid expansion (Dudley Declaration, ¶¶ 3-9). As explained by the Dudley Declaration, and as shown in Dudley 2001 and Yee, those methods repeatedly failed to produce objective, clinical results. Accordingly, one of ordinary skill in the art would have attempted to increase the number of rounds of rapid expansion, and would not have expected that administering T cells that had undergone *only one* round of rapid expansion would have resulted in superior, objective clinical responses. As explained in the Dudley Declaration, and as shown in Dudley 2002 and Dudley 2008, contrary to this expectation, administering T cells that had undergone *only one* round of rapid expansion did unexpectedly produce superior, objective clinical responses in patients (Dudley Declaration, ¶¶ 10-13) and answered a long-felt need in the art. Thus, because the claimed method answers a long-felt need, successfully treats cancer patients as compared to the repeated failure of other methods, and provides unexpectedly superior objective clinical responses as compared to the methods of Dudley 2001 and WO '239, the obviousness rejection cannot stand.

Since the final rejections of at least the sole rejected appealed independent claim are not supportable, the rejections should be withdrawn. Since all of the rejected appealed claims are commonly rejected, upon withdrawal of the rejections of appealed claim 23, appealed claims 24-40 should also be allowed.

Conclusion

For the reasons set forth above, Appellants respectfully submit that the rejections of the pending claims are improper and should be reversed.

Respectfully submitted,

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Date: 22 Dec. 2009

Appeal Brief (JMJ/SML/mlg)

Claims Appendix

23. A method of promoting the regression of a cancer in a mammal, which method comprises:

(i) administering to the mammal nonmyeloablative lymphodepleting chemotherapy, and

(ii) subsequently administering:

(a) autologous T-cells, which have been previously isolated and selected for highly avid recognition of an antigen of the cancer, the regression of which is to be promoted, by stimulation of the T-cells *in vitro* with the antigen of the cancer, followed by one cycle of rapid expansion using irradiated allogeneic feeder cells, OKT3 antibody, and IL-2, and, either concomitantly with the autologous T-cells or subsequently to the autologous T-cells, by the same route or a different route, a T-cell growth factor that promotes the growth and activation of the autologous T-cells, or

(b) autologous T-cells, which have been previously isolated, selected for highly avid recognition of an antigen of the cancer, the regression of which is to be promoted, by stimulation of the T-cells *in vitro* with the antigen of the cancer, and modified to express a T-cell growth factor that promotes the growth and activation of the autologous T-cells, followed by one cycle of rapid expansion using irradiated allogeneic feeder cells, OKT3 antibody, and IL-2, whereupon the regression of the cancer in the mammal is promoted.

24. The method of claim 23, wherein the T-cell growth factor is IL-2, IL-7, IL-15, or a combination of two or all of the foregoing.

25. The method of claim 23, wherein the nonmyeloablative lymphodepleting chemotherapy comprises the administration of cyclophosphamide and fludarabine.

26. The method of claim 25, wherein around 60 mg/kg of cyclophosphamide are administered for two days after which around 25 mg/m^2 fludarabine are administered for five days.

27. The method of claim 26, wherein the cyclophosphamide and fludarabine are administered intravenously.

28. The method of claim 24, wherein a dose of about 720,000 IU/kg of IL-2 is administered three times daily until tolerance.

29. The method of claim 28, wherein from about 5 to about 12 doses of IL-2 are administered.

30. The method of claim 29, wherein around 9 doses of IL-2 are administered.

31. The method of claim 28, wherein the dose of IL-2 is administered as a bolus intravenous injection.

32. The method of claim 23, wherein from about 1.2×10^{10} T-cells to about 4.3×10^{10} T-cells are administered.

33. The method of claim 23, wherein the T-cells are administered as an intravenous infusion.

34. The method of claim 33, wherein the intravenous infusion lasts approximately 30-60 min.

35. The method of claim 23, wherein the cancer is melanoma.

36. The method of claim 35, wherein the T-cells bind to MART-1 (SEQ ID NO: 1).

37. The method of claim 23, wherein the cancer is metastatic.

38. The method of claim 23, wherein the mammal is a human.

39. The method of claim 23, wherein the antigen of the cancer consists of amino acids 26-35 of MART-1 (SEQ ID NO: 1), in which amino acid 27 has been replaced with leucine.

40. The method of claim 23, wherein the antigen of the cancer is the gp100: 209-217 (210M) peptide (SEQ ID NO: 2).

Evidence Appendix

Exhibit A: Declaration under 37 C.F.R. § 1.132 by Dr. Mark E. Dudley (hereinafter, "Dudley Declaration"), filed on October 17, 2008;

Exhibit B: Yee et al., *PNAS,* 99: 16168-73 (2002);

Exhibit C: Dudley et al. *Science* 298: 850-854 (2002); and

Exhibit D: Dudley et al., *J. Clin. Oncol.*, 26(32): 5233-5239 (2008) referred to in the Dudley Declaration.

Exhibit A, including incorporated Exhibits B-D, were entered into the record in the Office Action dated December 17, 2008, at page 2, ¶ 6.

Related Proceedings Appendix

There are no related proceedings.